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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/981,289	10/15/2001	Bassil I. Dahiyat	A-68990-3/RFT/RMS/RMK	5268

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EXAMINER
SEHARASEYON, JEGATHEESAN

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/22/2002 13

Please find below and/or attached an Office communication concerning this application or proceeding.

RILEY

Office Action Summary	Application No.	Applicant(s)	
	09/981,289	DAHIYAT ET AL.	
	Examiner	Art Unit	
	Jegatheesan Seharaseyon	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 13-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 13-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 January 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8 & 11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election without traverse of Group I, claims 1-3 and 9, drawn to a TNF-α in Paper No. 10 (8/13/02) is acknowledged. Addition of claims 13-16 is also acknowledged. Further applicant has elected the species represented by variant Y115T (SEQ ID NO: 20) for examination in Paper No. 10 (8/13/02).

Specification

2. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Appropriate correction is required.

Drawings

4. In figure 8 and 9 the activity is reported in CPM. However, examples 2 and 3 indicate that the fluorescence was measured in each experiment. It is unclear what was measured. In addition, Applicant in figure 8 description of the drawing (page 4) states that variant E146K, was found to have agonistic activity similar to wild-type TNF-α. However, figure 8 seems to indicate that K112D to have wild type like activity and not E146K. Appropriate correction is required. The drawings have been objected by the draftsperson (see enclosed PTO 948).

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin.

2. **Corrections other than Informalities Noted by Draftsperson on form PTO-948.**

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.

Claim Rejections - 35 USC § 112, second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5a. Claims 1 and 16 rejected as vague and indefinite for reciting the term "variant", because the term "variant" is not defined in the specification. Therefore the metes and

bounds of these claims are unclear. This is because a variant may encompass a single amino acid change or several amino acid changes and it is unclear what "variants" are encompassed in this claim. In addition, Applicant appears to be claiming a product by what it is not rather than what it is. For example, Applicant claims the invention to be a non-naturally occurring variant TNF-α protein, but does not describe the variant. It is also not clear which of two receptor subtypes is involved in the receptor signaling.

Claim Rejections - 35 USC § 112, first paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6a. Claims 1 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a written description rejection.*

The specification discloses TNF-α substitutions at wild-type positions 21, 30, 31, 32, 33, 35, 65, 66, 67, 111, 112, 115, 140, 143, 144, 145, 146 and 147 (figure: 7). This meets the written description and enablement provisions of 35 USC 112, first paragraph. However, the specification does not disclose all possible variants of TNF-α. The claims as written, however, encompass TNF-α variant sequences which were not originally contemplated and fail to meet the written description provision of 35 USC 112,

first paragraph because the written description is not commensurate in scope with the recitation of claims 1 and 16. The specification does not provide written description to support the genus encompassed by the instant claims.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (*See Vas-Cath* at page 1116).

With the exception of isolated TNF-α polypeptide with substitutions at wild-type positions 21, 30, 31, 32, 33, 35, 65, 66, 67, 111, 112, 115, 140, 143, 144, 145, 146 and 147, the skilled artisan cannot envision all the detailed chemical structure of the claimed polypeptides, regardless of the complexity or simplicity of the method of isolation.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The polypeptide itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

Therefore, only the isolated TNF-α polypeptide with substitutions at wild-type positions 21, 30, 31, 32, 33, 35, 65, 66, 67, 111, 112, 115, 140, 143, 144, 145, 146 and 147, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. As a result, it does not appear that the inventors were in possession of various polypeptide sequences set forth in claims 1 and 16. Claims 2, 3, 13, 14 and 15 are rejected insofar as they depend on claim 1.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

6b. Claims 1 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for TNF-α variants K112D, Y115T, D143K, D143R, Y115I, D143E, A145R, A145K, A145E, E146K and E146R protein does not reasonably provide enablement for all variants TNF-α. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. See *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404. The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Despite knowledge in the art for producing variants of a given polypeptide with amino acid deletions, insertions or substitutions the specification fails to provide any guidance regarding the changes/modifications contemplated and yet retain the function of the TNF-α variants claimed. Furthermore, detailed information regarding the structural and functional requirements of the disclosed protein is lacking. Although it is accepted that the amino acid sequence of a polypeptide determines its structural and functional properties, predicting a protein's structure and function from mere sequence data remains an elusive task. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as

by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active variants, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. Therefore, predicting which variants would retain the functions of the protein is well outside the realm of routine experimentation. Thus, undue amount of experimentation would be required to generate changes/modifications contemplated and yet retain the function of the proteins claimed.

Applicants have not taught how one of skill in the art would use the full scope of polypeptide sequences encompassed by the invention of claims 1and 16. The specification as filed does not sufficiently teach one of skill in the art how to make and/or use the full scope of the claimed sequences. The amount of experimentation required to make and/or use the full scope of the claimed sequences would require trial and error experimentation to determine the functional sequences. Given the breadth of claims 1 and 16 in light of the unpredictability of the art as determined by the lack of working examples and shown by the prior at of record, the level of skill of the artisan, and the

lack of guidance provided in the instant specification, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention. Claims 2, 3, 13, 14 and 15 are rejected insofar as they depend on claim 1.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7a. Claims 1, 2, 14, 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Banner et al. (ref. A17 on the 1449).

The instant invention is directed to a non-naturally occurring variant TNF-α protein that has at least one amino acid substitution as compared to the wild –type TNF-α sequence forming mixed trimers of TNF-α incapable of activating receptor signaling.

Banner et al. teaches the production of mutations at several different amino acid positions compared to the wild-type TNF-α, which has different binding affinity to p55-TNF receptor compared to p75 TNF receptor (abstract). Amino acid substitutions have been made at 33, 34, 65, 67, 75, 143, 145 and 147, including the following changes: D143N, D143E, A145R and A145K. It also teaches multiple amino acid substitutions compared to wild-type TNF-α sequence, including at least 3 amino acid substitutions (columns 5 and 6). They also teach the recovery of the non-naturally occurring variant proteins (columns 17 and 18). Although Banner et al., does not explicitly teach the formation of mixed trimer formation due the presence of variant TNF-α, thus affecting

the activation of receptor signaling, the inability of activating receptor signaling is an inherent function of a mixed TNF-α timer. Therefore, the disclosure of Banner et al. anticipates claims 1, 2, 14, 15 and 16. Claims 3 and 13 are rejected insofar as they depend on rejected claim 1.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8a. Claims 3 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Banner et al. (ref. A17 on the 1449).

The instant invention is directed to a non-naturally occurring variant TNF-α protein that has at least one amino acid substitution as compared to the wild –type TNF-α sequence forming mixed trimers TNF-α incapable of activating receptor signaling.

Specifically, Applicant intends to have the following substitutions selected from K112D, Y115T, D143K and Y115I as variants.

Banner et al. teaches the production of mutations at several different amino acid positions compared to the wild-type TNF-α, which has different binding affinity to p55-TNF receptor compared to p75 TNF receptor (abstract). However, they do not describe the generation of substitutions selected from K112D, Y115T, D143K and Y115. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods disclosed in Banner et al. to generate the various substitutions of the instant invention. One of ordinary skill would have been motivated with reasonable expectation of success to modify the methods of Banner et al. because variants of TNF-α generated form mixed trimers that make the TNF incapable of activating receptor signaling. Therefore, the instant invention is prima facie obvious over Banner et al. (ref. A17 on the 1449).

9. No claims are allowable.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon, Ph.D whose telephone number is 703-305-1112. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-0294 for regular communications and 703-308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

JS
October 21, 2002

JEFFREY STUCKER
PRIMARY EXAMINER